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This letter to the editor involves a novel application of The Energy Depletion Model of heatstroke pathophysiology, developed two years ago in the Heat Research Division, USARIEM. This application is made to cocaine intoxication, as reported by Roth et al. (NEJM 319:673-677, 1988) in a recent publication. The Energy Depletion Model is briefly described, five salient reasons are given in support of this application to cocaine intoxication, and future research implications are presented.

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Application of a model of exertional heatstroke pathophysiology to cocaine intoxication

To the Editor, New England Journal of Medicine:

We would like to propose a novel cellular model of cocaine intoxication which originates from work on heatstroke pathophysiology[1,2]. This model emphasizes the role of heat, hypohydration (hypernatremia), and increased neuromuscular activity (i.e. accelerated energy consumption, ion flux, and heat production) in activating the sodium pump. A vicious circle is described which leads to increased intracellular sodium concentration, cell swelling, hyperthermia, energy depletion, metabolic cascades, and irreversible cell damage. Named The Energy Depletion Model, it shifts emphasis from hyperthermia alone to a potential cellular mechanism implicating anaerobic glycolysis and lactacidosis as consequences of the total energy drain on the cell.

For the following reasons, we propose that *this model is applicable to cocaine* intoxication. (1) Exertional heatstroke[2,3,9] and cocaine intoxication[4,5] share many of the same symptoms (Table 1), strongly implicating common pathways during the evolution of each disorder. The symptoms of both illnesses (e.g. elevated serum ALT, AST, CPK; myoglobinuria) suggest increased ion flux, membrane permeability to macromolecules, and thereby a potential increase in permeability to smaller molecular species such as monovalent and divalent cations. (2) We believe that many of the systemic consequences associated with heatstroke have their origin in conditions leading to increased cell permeability and energy depletion[2]. If the commonality of the symptoms between heatstroke and cocaine intoxication involves similar events at this level of structure and function, then the many applications of heat illness modelling could provide new avenues of research for studying cocaine abuse in a performance-based animal model[1]. (3) By definition, muscular exercise is an important factor in exertional heatstroke[1,2,3,9]. Similarly, myoclonus, status

epilepticus, and excessive heat production have been reported following pharmacologic doses of cocaine, amphetamine, phencyclidine (PCP), alcohol, and lithium[4,5,7]. These drug-induced states result in many of the symptoms[5,6,7,8] described in Table 1, and should be included among the differential diagnoses[3,5] in cases of suspected cocaine intoxication and exertional heatstroke. (4) The non-pyrogenic hyperthermia (> 40°C) characteristic of cocaine intoxication[4] (Table 1) agrees well with this model. (5) This model predicts a decreased serum calcium level[4] (Table 1), theoretically the result of membrane depolarization, dissipation of the sodium gradient, and ATP depletion, which facilitate calcium sequestration within the cell.

Although we have no plans to directly investigate or model cocaine intoxication, we welcome correspondence regarding The Energy Depletion Model[1,2] from those who do.

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Table 1 - Selected signs and symptoms which may be observed in severe cases of heatstroke[2,3,9] and cocaine intoxication[4,5].

Signs and Symptoms	Cocaine intoxication	Heatstroke
combative behavior	+	+
coma	+	+
nonpyrogenic hyperthermia (> 40°C)	+	+
acute renal failure	+	+
oliguria (< 400ml/24hr)	+	+
hyperuricemia	+	+
rhabdomyolysis	+	+
hypotension	+	+
seizure	+	+
myocardial and/or hepatic damage	+	+
elevated serum ALT, AST, CPK, bilirubin	+	+
myoglobinuria	+	+
serum hypocalcemia	+	+
disseminated intravascular coagulation	+	+
multi-organ hemorrage	+	+

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